PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM.70590/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03297	30/08/2000	04/09/1999
International Patent Classification (IPC) or national classification and IPC C07C211/32		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/03/2001	27.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herzog, A Telephone No. +49 89 2399 8033

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03297

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-44 as originally filed

Claims, No.:

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1(part),3-7(part).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1(part),3-7(part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8
	No:	Claims	1-7,9-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

As already stated in the International Search Report (see Further Information Sheet PCT/ISA/210), the initial phase of the search revealed a very large number of documents relevant to the issue of novelty for present claims 1 and 3-7 due to the fact that these claims relate to an extremely large number of possible compounds.
So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).
The search thus has been restricted to the subject-matter of claim 2 and all examples described in the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application relates to compounds which elevate pyruvate dehydrogenase (PDH) activity (claims 1-8 and 11), processes for their preparation (claim 9), pharmaceutical compositions containing them (claim 10) as well as to the use of said compounds in the manufacture of a medicament (claim 12). The medicament can be used in the treatment of diabetes mellitus, peripheral vascular disease and myocardial

ischaemia.

As already mentioned in Re Item III, the search had to be restricted to the subject-matter of claim 2 and all examples described in the application.
The examination will be carried out for the subject-matter which has been searched only, namely those parts relating to the **compounds according to formula (I) of claim 1 wherein one of R^1** and R^2 is methyl and the other is trifluoromethyl.

D1: XP002122777 (Aicher, T.D. et al., J. Med. Chem., vol. 42, no. 15 (1999), p. 2741- 2746; ISSN: 0022-2623)

1. The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of present claims 1-7 and 9-12 is not new.

   The compounds 3l, 3n, 3o, 3q and 3r in Scheme 3 on page 2742 in D1 fall within present formula (I). In the proviso in claim 1 (cf. page 47, lines 16-19), the Applicant excluded some compounds by disclaimer. However, the compounds 3n and 3o have not been disclaimed (the methyl group is in the **3**-position of the piperazinyl ring!) and thus are still novelty-destroying for present claims 1-7 and 9-12.
   Moreover, the proviso is not clear (see **Re Item VIII**, 1.), and thus other compounds in D1 might be novelty-destroying as well.

   The compounds disclosed in present claim 8 are not disclosed in the available prior art.

2. The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of present claims 1-12 does not involve an inventive step for the following reasons:

2.1 It is observed that in all the examples in the present specification (Examples 1-

27), the variables R^1, R^2, R^3, A and n in formula (I) have the meaning defined in claims 2-7 or in the description on page 14, lines 6-18, i.e.

- one of R^1 and R^2 is methyl and the other is trifluoromethyl;
- ring A is piperidyl, piperazinyl of indolinyl, wherein said piperazinyl is optionally substituted on nitrogen by R^4-D-;
- R^3 is a substituent on carbon and is selected from amino, methyl, 4-mesylphenylsulphonyl, 4-methylthiophenylthio, 4-fluorobenzoyl and 4-cyanobenzoylamino;
- R^4 is C_{1-4}alkyl, phenyl (optionally substituted with one or more t-butyl, isopropyl, nitro, halo, N,N-dimethylcarbamoyl, N,N-dimethylamino, 2-hydroxyethylamino, cyano, acetyl, methoxy or carboxy) or thienyl;
- D is $-SO_2-$ or -C(O)-; and
- n is 0 to 3.

Compounds of present formula (I) wherein said variables have a meaning other than the above-listed thus are not supported by the description and examples as required by Article 6 PCT, i.e. in addition no evidence is given which could prove that these compounds solve the problem posed (Article 33(3) PCT).

2.2 On pages 23-26, several methods for the assessment of the activity of compounds are described. However, **none of the compounds** disclosed in the present invention has been tested. It is thus not clear whether the presently claimed compounds are able to elevate the PDH activity and thus solve the problem posed (Article 33(3) PCT). Without any data which could prove the activity of the presently claimed compounds, an inventive step cannot be acknowledged.

2.3 As already mentioned in 1. above, compounds wherein
one of R^1 and R^2 is methyl and the other is trifluoromethyl,
the ring A represents piperazinyl wherein the second nitrogen is unsubstituted or substituted by p-cyanobenzoyl, benzyloxycarbonyl or benzyl,
the variable n represents 0, 1 or 2 and
R^3, if present, represents methyl
are already known from D1 (cf. D1, page 2742, Scheme 3).

The compounds of the present invention wherein the ring A also represents piperazinyl differ from the compounds in D1 only in the substituent connected to the second nitrogen atom in 4-position of the ring. However, since the substituent obviously can be varied as shown in D1, these differences are considered minor, and thus no inventive skill is required to get to these compounds of the present application (Article 33(3) PCT).

Re Item VI

Certain documents cited

D2: XP000979112 (Mann, W.R. et al., Biochim. Biophys. Acta (2000), 1480(1-2), p. 283-292)

D3: XP002158429 (Aicher, T.D. et al., J. Med. Chem., vol. 43, no. 2 (27 January 2000), p. 236-249)

Special reference is made to
D2: compound 5 in Figure 1 (page 284);
D3: Scheme 2 (page 239); Table 1 (page 240), compounds 4t, 4v; Table 2 (page 241), compounds 10-16.

Re Item VIII

Certain observations on the international application

1. In claim 1, the variable R^3 is defined as a substituent on carbon. In addition, Ring A is defined as a nitrogen-linked mono- or bicyclic heterocyclic ring wherein if said heterocyclic group contains a -NH- moiety (as e.g. in a piperazine ring) that nitrogen is optionally substituted by R^4-D-. However, in the proviso in claim 1 (cf. page 47, lines 16-19), the compounds i), ii), iv), v) and vii) are disclaimed wherein a substituent R^3 seems to be present also in 4-position of the piperazine ring.

Since according to the definition of R^3, said substituent is connected to a carbon atom only, the scope of the claims is not clear (Article 6 PCT).
In addition, the position of the cyano group in the cyanobenzoyl substituent in the disclaimed compounds i), iv) and vii) is not defined (Article 6 PCT).

2. In claims 8 and 9, the expression "according to claim 1" should be inserted after "A compound of formula (I)" since said formula or the variables therein are not explained in said claims 8 and 9 (Article 6 PCT).

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 May 2001 (21.05.01)	
International application No. PCT/GB00/03297	**Applicant's or agent's file reference** PHM.70590/WO
International filing date (day/month/year) 30 August 2000 (30.08.00)	**Priority date** (day/month/year) 04 September 1999 (04.09.99)
Applicant BUTLIN, Roger, John et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 March 2001 (26.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

LCP

WO 01/17942
PCT/GB00/03297

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272, Mereside
Alderley Park, Macclesfield
Cheshire SK10 4GR
ROYAUME-UNI

CODE	DATE	NTD

RECD 26 MAR 2001 GIPS

DATA ENTERED JRZ/F.L.

FINAL CHECK RMJ

Date of mailing (day/month/year) 15 March 2001 (15.03.01)	
Applicant's or agent's file reference PHM.70590/WO OK	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/GB00/03297 OK	30 August 2000 (30.08.00)	04 September 1999 (04.09.99)

Applicant
ASTRAZENECA AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,FI,
   GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,
   MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   15 March 2001 (16.03.01) under No. WO 01/17942

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

Th International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

3883401

Continuation f Form PCT/IB/3[redacted]

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
15 March 2001 (15.03.01)	
Applicant's or agent's file reference	**International application No.**
PHM.70590/WO	PCT/GB00/03297

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17942 A1

(51) International Patent Classification[7]: C07C 211/32, C07D 295/22, 295/18, 209/08, 211/58, A61K 31/495, A61P 3/10

(21) International Application Number: PCT/GB00/03297

(22) International Filing Date: 30 August 2000 (30.08.2000)

(25) Filing Language: English

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(30) Priority Data:
9920821.7 4 September 1999 (04.09.1999) GB
9929835.8 18 December 1999 (18.12.1999) GB

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BUTLIN, Roger, John** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **PEASE, Janet, Elizabeth** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **BLOCK, Michael, Howard** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **NOWAK, Thorsten** [DE/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **BURROWS, Jeremy, Nicholas** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **CLARKE, David, Stephen** [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: **BRYANT, Tracey**; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

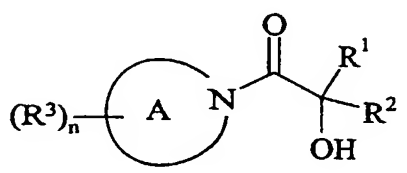
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/17942 A1

(54) Title: AMIDES AS INHIBITORS FOR PYRUVATE DEHYDROGENASE



(I)

(57) Abstract: A compound of formula (I) wherein: Ring A is a nitrogen linked mono or bicyclic heterocyclic ring as defined within; R^1 and R^2 are independently C_{1-3}alkyl optionally substituted by fluoro or chloro; or R^1 and R^2 together with the carbon atom to which they are attached, form a C_{3-5}cylcoalkyl ring optionally substituted by fluoro; R^3 is as defined within; and n is 0-5; wherein the values of R^3 may be the same or different; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof is described. The use of compounds of formula (I) in the production of an elevation of PDH activity in a warm-blooded animal such as a human being are also described. Pharmaceutical compositions, methods and processes for preparation of compounds of formula (I) are detailed.

AMIDES AS INHIBITORS FOR PYRUVATE DEHYDROGENASE

The present invention relates to compounds which elevate pyruvate dehydrogenase (PDH) activity, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with reduced PDH activity, to their use as medicaments and to their use in the manufacture of medicaments for use in the elevation of PDH activity in warm-blooded animals such as humans, in particular the treatment of diabetes mellitus, peripheral vascular disease and myocardial ischaemia in warm-blooded animals such as humans, more particularly to their use in the manufacture of medicaments for use in the treatment of diabetes mellitus in warm-blooded animals such as humans.

Within tissues adenosine triphosphate (ATP) provides the energy for synthesis of complex molecules and, in muscle, for contraction. ATP is generated from the breakdown of energy-rich substrates such as glucose or long chain free fatty acids. In oxidative tissues such as muscle the majority of the ATP is generated from acetyl CoA which enters the citric acid cycle, thus the supply of acetyl CoA is a critical determinant of ATP production in oxidative tissues. Acetyl CoA is produced either by β-oxidation of fatty acids or as a result of glucose metabolism by the glycolytic pathway. The key regulatory enzyme in controlling the rate of acetyl CoA formation from glucose is PDH which catalyses the oxidation of pyruvate to acetyl CoA and carbon dioxide with concomitant reduction of nicotinamide adenine dinucleotide (NAD) to NADH.

In disease states such as both non-insulin dependent (NIDDM) and insulin-dependent diabetes mellitus (IDDM), oxidation of lipids is increased with a concomitant reduction in utilisation of glucose, which contributes to the hyperglycaemia. Reduced glucose utilisation in both IDDM and NIDDM is associated with a reduction in PDH activity. In addition, a further consequence of reduced PDH activity may be that an increase in pyruvate concentration results in increased availability of lactate as a substrate for hepatic gluconeogenesis. It is reasonable to expect that increasing the activity of PDH could increase the rate of glucose oxidation and hence overall glucose utilisation, in addition to reducing hepatic glucose output. Another factor contributing to diabetes mellitus is impaired insulin secretion, which has been

shown to be associated with reduced PDH activity in pancreatic β-cells (in a rodent genetic model of diabetes mellitus Zhou et al. (1996) Diabetes 45: 580-586).

Oxidation of glucose is capable of yielding more molecules of ATP per mole of oxygen than is oxidation of fatty acids. In conditions where energy demand may exceed energy supply, such as myocardial ischaemia, intermittent claudication, cerebral ischaemia and reperfusion, (Zaidan et al., 1998; J. Neurochem. 70: 233-241), shifting the balance of substrate utilisation in favour of glucose metabolism by elevating PDH activity may be expected to improve the ability to maintain ATP levels and hence function.

An agent which is capable of elevating PDH activity may also be expected to be of benefit in treating conditions where an excess of circulating lactic acid is manifest such as in certain cases of sepsis.

The agent dichloroacetic acid (DCA) which increases the activity of PDH after acute administration in animals, (Vary et al., 1988; Circ. Shock, 24: 3-18), has been shown to have the predicted effects in reducing glycaemia, (Stacpoole et al., 1978; N. Engl. J. Med. 298: 526-530), and as a therapy for myocardial ischaemia (Bersin and Stacpoole 1997; American Heart Journal, 134: 841-855) and lactic acidaemia, (Stacpoole et al., 1983; N. Engl. J. Med. 309: 390-396).

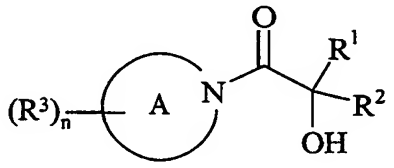
PDH is an intramitochondrial multienzyme complex consisting of multiple copies of several subunits including three enzyme activities E1, E2 and E3, required for the completion of the conversion of pyruvate to acetyl CoA (Patel and Roche 1990; FASEB J., 4: 3224-3233). E1 catalyses the non-reversible removal of CO_2 from pyruvate; E2 forms acetyl CoA and E3 reduces NAD to NADH. Two additional enzyme activities are associated with the complex: a specific kinase which is capable of phosphorylating E1 at three serine residues and a loosely-associated specific phosphatase which reverses the phosphorylation. Phosphorylation of a single one of the three serine residues renders the E1 inactive. The proportion of the PDH in its active (dephosphorylated) state is determined by a balance between the activity of the kinase and phosphatase. The activity of the kinase may be regulated *in vivo* by the relative concentrations of metabolic substrates such as NAD/NADH, CoA/acetylCoA and adenine diphosphate (ADP)/ATP as well as by the availability of pyruvate itself.

European Patent Publication Nos. 617010 and 524781 describes compounds which are capable of relaxing bladder smooth muscle and which may be used in the treatment of urge

incontinence. We have found that the compounds of the present invention are very good at elevating PDH activity, a property nowhere disclosed in EP 0617010 and EP 524781.

The present invention is based on the surprising discovery that certain compounds elevate PDH activity, a property of value in the treatment of disease states associated with disorders of glucose utilisation such as diabetes mellitus, obesity, (Curto et al., 1997; Int. J. Obes. 21: 1137-1142), and lactic acidaemia. Additionally the compounds may be expected to have utility in diseases where supply of energy-rich substrates to tissues is limiting such as peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, muscle weakness, hyperlipidaemias and atherosclerosis (Stacpoole et al., 1978; N. Engl. J. Med. 298: 526-530). A compound that activates PDH may also be useful in treating Alzheimer's disease (AD) (J Neural Transm (1998) 105, 855-870).

Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

Ring A is a nitrogen linked mono or bicyclic heterocyclic ring; wherein if said heterocyclic group contains an -NH- moiety that nitrogen is optionally substituted by R^4-D-;

R^1 and **R^2** are independently $C_k$alkyl optionally substituted by 1 to 2k+1 atoms selected from fluoro and chloro wherein k is 1-3;

or R^1 and R^2 together with the carbon atom to which they are attached, form a $C_m$cycloalkyl ring optionally substituted by 1 to 2m-2 fluorine atoms wherein m is 3-5;

R^3 is a substituent on carbon and is halo, hydroxy, cyano, formyl, amino, nitro, carboxy, carbamoyl, ureido, thiol, sulphamoyl or R^5-E-;

R^4 is C_{1-6}alkyl, phenyl or a heterocyclic group, wherein in R^4 any C_{1-6}alkyl, phenyl or heterocyclic groups (on a ring carbon) may be optionally substituted by one or more R^6 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8;

D is -C(O)-, -N(R^9)C(O)-, -S(O)$_2$-, -NS(O)$_2$-, -OC(O)- or D is a direct bond;

R^5 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, phenyl, naphthyl or a heterocyclic group, wherein in R^5 any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, phenyl, naphthyl or heterocyclic groups (on a ring carbon) may be optionally substituted by one or more R^6 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8;

E is -O-, -N(R^9)-, -C(O)-, -N(R^9)C(O)-, -C(O)N(R^9)-, -S(O)$_a$- wherein a is 0-2, -OC(O)-, -C(O)O-, -N(R^9)C(O)O-, -OC(O)N(R^9)-, -C(S)N(R^9)-, -N(R^9)C(S)-, -SO_2N(R^9)-, -N(R^9)SO_2-, -N(R^9)C(O)N(R^9)-, -N(R^9)C(S)N(R^9)-, -SO_2NHC(O)-, -SO_2N(R^9)C(O)-, -C(O)NHSO_2- or E is a direct bond;

R^6 is trifluoromethyl, C_{1-6}alkyl, halo, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, formyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, *N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(*N*-C_{1-6}alkyl)amino, nitro, carboxy, carbamoyl, C_{1-6}alkoxycarbonyl, thiol, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$aminosulphonyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, ureido, *N'*-(C_{1-6}alkyl)ureido or *N'*-(C_{1-6}alkyl)$_2$ureido, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl, naphthyl, phenyl or a heterocyclic group wherein in R^6 any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cylcoalkyl, naphthyl, phenyl or heterocyclic groups (on a ring carbon) may be optionally substituted by one or more R^7 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8;

R^7 is trifluoromethyl, cyano, C_{1-6}alkyl, halo, hydroxy, trifluoromethoxy, C_{1-6}alkoxy, formyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, *N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(*N*-C_{1-6}alkyl)amino, nitro, carboxy, carbamoyl, C_{1-6}alkoxycarbonyl, thiol, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$aminosulphonyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl or a heterocyclic group (optionally substituted by one or more R^{11}), and wherein in R^7 any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cylcoalkyl groups may be optionally substituted by one or more groups selected from R^{12};

R^8 is C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzoyl, (heterocyclic group)carbonyl,

phenylsulphonyl, (heterocyclic group)sulphonyl, phenyl or a carbon linked heterocyclic group, and wherein in R^8 any C_{1-6}alkyl, phenyl or heterocyclic group (on a ring carbon) may be optionally substituted by one or more R^6, and if a heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R^9 is hydrogen or C_{1-6}alkyl optionally substituted by one or more R^{10} with the proviso that R^{10} is not a substituent on the carbon attached to a nitrogen atom;

R^{10} is halo, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, *N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(*N*-C_{1-6}alkyl)amino, C_{1-6}alkylsulphonylamino, C_{1-6}alkylsulphonyl(*N*-C_{1-6}alkyl)amino, thiol, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$aminosulphonyl, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl or formyl;

R^{11} is C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxyC_{1-6}alkanoyl, phenylC_{1-6}alkyl, benzoyl, phenylC_{1-6}alkanoyl, phenylC_{1-6}alkoxycarbonyl or phenylsulphonyl and wherein in R^{11} any C_{1-6}alkyl group can be optionally substituted by one or more R^{13};

R^{12} is halo, hydroxy, *N*-methylpiperazinyl, *N*-acetylpiperazinyl, morpholino, piperidino, cyano, amino, *N,N*-dimethylamino, acetamido, carbamoyl, carboxy, methanesulphonyl or sulphamoyl;

R^{13} is halo, hydroxy, cyano, amino, *N,N*-dimethylamino, acetamido, carbamoyl, carboxy, methanesulphonyl or sulphamoyl;

n is 0-5; wherein the values of R^3 may be the same or different;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

with the proviso that if R^1 is methyl, R^2 is trifluoromethyl and Ring A is piperazin-1-yl then $(R^3)_n$ is not i) 4-cyanobenzoyl, ii) 2-methyl-4-benzyloxycarbonyl, iii) 2-methyl, iv) 2-methyl-4-cyanobenzoyl, v) 2,5-dimethyl-4-benzyl, vi) 2,5-dimethyl or vii) 2,5-dimethyl-4-cyanobenzoyl.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" includes C_{1-4}alkyl, methyl, ethyl, propyl,

isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. The term "halo" refers to fluoro, chloro, bromo and iodo. Where a phrase such as "any C_{1-6}alkyl group may be optionally substituted by one or more groups" for the avoidance of doubt, it is to be understood that this refers to all groups that contain a C_{1-6}alkyl group, for example this phrase would also relate to a C_{1-6}alkanoyl group if that was listed in the paragraph.

A "nitrogen linked mono or bicyclic heterocyclic ring" is a saturated, partially saturated or fully unsaturated, mono or bicyclic ring containing 4-12 atoms, one atom of which is a nitrogen atom (attached to form an amide as shown) and the other atoms are either all carbon atoms or they are carbon atoms and 1-3 heteroatoms chosen from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and a ring nitrogen and/or sulphur atom may be optionally oxidised to form the *N*-oxide and or the S-oxides. It will be appreciated that in forming this nitrogen link, the nitrogen atom is not quaternised, i.e. a neutral compound is formed.

A "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and a ring nitrogen and/or sulphur atom may be optionally oxidised to form the *N*-oxide and or the S-oxides. Suitable values for a "heterocyclic group" include morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkylsulphanyl" include methylthio and ethylthio. Examples of "C_{1-6}alkylsulphinyl" include methylsulphinyl and ethylsulphinyl. Examples of "C_{1-6}alkylsulphonyl" include C_{1-4}alkylsulphonyl, mesyl and

ethylsulphonyl. Examples of "C_{1-6}alkylsulphonylamino" include C_{1-4}alkylsulphonylamino, mesylamino and ethylsulphonylamino. Examples of "C_{1-6}alkanoyl" include C_{1-4}alkanoyl, propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" include methylamino and ethylamino. Examples of "*N*-(C_{1-6}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{3-6}cycloalkyl" are cyclopropyl and cyclohexyl. Examples of "C_{2-6}alkenyl" are C_{2-4}alkenyl, vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are C_{2-4}alkynyl, ethynyl, 1-propynyl and 2-propynyl. Examples of "C_{1-6}alkanoyl(*N*-C_{1-6}alkyl)amino" are C_{1-4}alkanoyl(*N*-C_{1-4}alkyl)amino, (*N*-methyl)formamido and (*N*-propyl)acetamido. Examples of "*N*-(C_{1-6}alkyl)aminosulphonyl" are *N*-(C_{1-4}alkyl)aminosulphonyl, *N*-(methyl)aminosulphonyl and *N*-(ethyl)aminosulphonyl. Examples of "*N*-(C_{1-6}alkyl)$_2$aminosulphonyl" are *N*-(C_{1-4}alkyl)$_2$aminosulphonyl, *N*-(dimethyl)aminosulphonyl and *N*-(methyl)-*N*-(ethyl)aminosulphonyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-(C_{1-4}alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N*-(C_{1-6}alkyl)$_2$carbamoyl" are *N*-(C_{1-4}alkyl)$_2$carbamoyl, dimethylaminocarbonyl and *N*-methyl-*N*-ethylaminocarbonyl. Examples of "(heterocyclic group)carbonyl" are pyrid-3-ylcarbonyl and pyrimid-2-ylcarbonyl. Examples of "(heterocyclic group)sulphonyl" are pyrid-3-ylsulphonyl and pyrimid-2-ylsulphonyl. Examples of "C_{1-6}alkoxyC_{1-6}alkanoyl" include ethoxypropionyl and methoxyacetyl. Examples of "phenylC_{1-6}alkyl" include phenethyl and benzyl. Examples of "phenylC_{1-6}alkanoyl" include 3-phenylpropionyl and phenacetyl. Examples of "phenylC_{1-6}alkoxycarbonyl" include benzyloxyoxycarbonyl and 2-phenylethoxycarbonyl. Examples of "*N'*-(C_{1-6}alkyl)ureido" are *N'*-methylureido and *N'*-ethylureido. Examples of "*N'*-(C_{1-6}alkyl)$_2$ureido" are *N',N'*-dimethylureido and *N'*-methyl-*N'*-ethylureido.

Preferred values of Ring A, R^1, R^2, R^3 and n are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Preferably Ring A is morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolidinyl, indolyl, isoindolyl, isoindolinyl, indolinyl, benzimidazolyl, purinyl, 1,2,3,4-4H-isoquinolinyl and triazolyl wherein if any of these rings contain an -NH- moiety that nitrogen is substituted by R^4-D-.

More preferably Ring A is piperidyl, piperazinyl, pyrrolidinyl, pyrrolinyl, homopiperazinyl, indolinyl, 1,2,3,4-4H-isoquinolinyl and isoindolinyl.

Particularly Ring A is piperidyl, piperazinyl, pyrrolidinyl, pyrrolinyl, indolinyl, 1,2,3,4-4H-isoquinolinyl and isoindolinyl.

More particularly Ring A is piperidyl, piperazinyl or indolinyl.

In one aspect of the invention preferably Ring A is piperazinyl.

In another aspect of the invention preferably Ring A is piperidyl, pyrrolidinyl, pyrrolinyl, indolinyl, 1,2,3,4-4H-isoquinolinyl and isoindolinyl.

In another aspect of the invention more preferably Ring A is piperidyl or indolinyl.

In a further aspect of the invention, preferably Ring A is piperidyl, piperazinyl or indolinyl; wherein said piperazinyl is optionally substituted on nitrogen by R^4-D-;

R^4 is C_{1-4}alkyl, phenyl {optionally substituted with one or more *t*-butyl, isopropyl, nitro, halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, cyano, acetyl, methoxy or carboxy} or thienyl; and

D is $-SO_2-$ or -C(O)-.

In one aspect of the invention R^1 and R^2 are independently $C_k$alkyl optionally substituted by from 1 to 2k+1 atoms selected from fluoro and chloro wherein k is 1-3.

Preferably R^1 and R^2 are independently $C_k$alkyl optionally substituted by from 1 to 2k+1 atoms selected from fluoro and chloro, wherein k is 1-3,

or R^1 and R^2, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

More preferably R^1 and R^2 are independently $C_k$alkyl optionally substituted by from 1 to 2k+1 fluorine atoms, wherein k is 1-2,

or R^1 and R^2, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

Particularly R^1 and R^2 are independently methyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and perfluoroethyl,

or R^1 and R^2, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

More particularly R^1 and R^2 are independently methyl, fluoromethyl, difluoromethyl and trifluoromethyl,

or R^1 and R^2, together with the carbon atom to which they are attached, form a cyclopropane ring optionally substituted by from 1 to 4 fluorine atoms.

Preferred combinations of R^1 and R^2 are as follows.

Preferably R^1 and R^2 are both methyl or one of R^1 and R^2 is methyl and the other is trifluoromethyl.

More preferably one of R^1 and R^2 is methyl and the other is trifluoromethyl.

Preferably R^4 is C_{1-4}alkyl, phenyl or a heterocyclic group, wherein in R^4 any C_{1-4}alkyl, or a heterocyclic group (on a ring carbon) may be optionally substituted by one or more R^5 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8.

More preferably R^4 is C_{1-4}alkyl {optionally substituted with one or more hydroxy, acetamido, methoxy, carbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino or mesyl}, phenyl {optionally substituted with one or more halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, *N*-methylpiperazinyl, *N*-acetylpiperazinyl, *N*-mesylpiperazinyl, amino, methanesulphinyl, acetamido, mesyl} or a heterocyclic group {where if the heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted with methyl, mesyl or acetyl} which heterocyclic group may be optionally substituted with one or more methyl, halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, *N*-methylpiperazinyl, *N*-acetylpiperazinyl, *N*-mesylpiperazinyl, amino, methanesulphinyl, acetamido, methanesulphonyl.

Particularly R^4 is ethyl, 4-mesylphenyl, 4-methylthiophenyl, 4-carboxyphenyl, 4-(*N,N*-dimethylcarbamoyl)phenyl, 4-fluorophenyl, 4-(2-hydroxyethylamino)phenyl, 4-cyanophenyl, 2-chloro-4-cyanophenyl, 4-acetylphenyl, 4-methoxyphenyl, 4-(*N,N*-dimethylamino)phenyl, 4-bromophenyl or thien-2-yl.

In another aspect of the invention, more preferably R^4 is C_{1-4}alkyl, phenyl {optionally substituted with one or more *t*-butyl, isopropyl, nitro, halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, cyano, acetyl, methoxy or carboxy} or thienyl.

In an additional aspect of the invention, more preferably R^4 is phenyl optionally substituted with one or more halo, *N,N*-dimethylcarbamoyl, 2-hydroxyethylamino, cyano, methoxy or carboxy.

Preferably D is -C(O)-, -N(R^9)C(O)-, -S(O)$_2$- or -NS(O)$_2$- or D is a direct bond.

More preferably D is $-N(R^9)C(O)-$, $-S(O)_2-$ or $-NS(O)_2-$ or D is a direct bond.

Particularly D is $-SO_2-$ or $-C(O)-$.

Preferably R^4-D- is C_{1-4}alkylsulphonyl optionally substituted by one or more R^6, phenylsulphonyl optionally substituted by one or more R^6 or thienylsulphonyl optionally substituted by one or more R^6.

In another aspect of the invention preferably R^4-D- is C_{1-4}alkylsulphonyl optionally substituted by one or more R^6, phenylcarbonyl optionally substituted by one or more R^6, phenylsulphonyl optionally substituted by one or more R^6 or thienylsulphonyl optionally substituted by one or more R^6.

More preferably R^4-D- is ethylsulphonyl, 4-carboxyphenylsulphonyl, 4-(N,N-dimethylcarbamoyl)phenylsulphonyl, 4-fluorophenylsulphonyl or thien-2-ylsulphonyl.

In another aspect of the invention more preferably R^4-D- is ethylsulphonyl, 4-carboxyphenylsulphonyl, 4-(*N,N*-dimethylcarbamoyl)phenylsulphonyl, 4-fluorophenylsulphonyl, 4-fluorophenylcarbonyl or thien-2-ylsulphonyl.

In a further aspect of the invention more preferably R^4-D- is ethylsulphonyl, 4-carboxyphenylsulphonyl, 4-(*N,N*-dimethylcarbamoyl)phenylsulphonyl, 4-fluorophenylsulphonyl, 4-fluorobenzoyl, thien-2-ylsulphonyl, 4-(*N,N*-dimethylcarbamoyl)benzoyl, 4-(2-hydroxyethylamino)phenylsulphonyl, 4-cyanophenylsulphonyl, 2-chloro-4-cyanophenylsulphonyl, 4-acetylphenylsulphonyl, 4-methoxyphenylsulphonyl, 4-methoxybenzoyl, 4-(*N,N*-dimethylamino)benzoyl, 4-bromophenylsulphonyl or 4-bromobenzoyl.

In an additional aspect of the invention more preferably R^4-D- is ethylsulphonyl, 4-carboxyphenylsulphonyl, 4-(*N,N*-dimethylcarbamoyl)phenylsulphonyl, 4-fluorophenylsulphonyl, 4-fluorobenzoyl, thien-2-ylsulphonyl, 4-(*N,N*-dimethylcarbamoyl)benzoyl, 4-(2-hydroxyethylamino)phenylsulphonyl, 4-cyanophenylsulphonyl, 2-chloro-4-cyanophenylsulphonyl, 4-acetylphenylsulphonyl, 4-methoxyphenylsulphonyl, 4-methoxybenzoyl, 4-(*N,N*-dimethylamino)benzoyl, 4-bromophenylsulphonyl, 4-bromobenzoyl, 4-*t*-butylbenzoyl, 4-isopropylphenylsulphonyl or 2-nitrophenylsulphonyl.

In an additional aspect of the invention particularly R^4-D- is 4-carboxyphenylsulphonyl, 4-(*N,N*-dimethylcarbamoyl)phenylsulphonyl, 4-fluorophenylsulphonyl, 4-(2-hydroxyethylamino)phenylsulphonyl, 4-cyanophenylsulphonyl or 4-methoxyphenylsulphonyl.

Preferably R^5 is C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, phenyl or a heterocyclic group, wherein in R^5 any C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, phenyl or heterocyclic group (on a ring carbon) may be optionally substituted by one or more R^6 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8.

More preferably R^5 is C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, phenyl or a heterocyclic group, wherein in R^5 any C_{1-4}alkyl, C_{2-4}alkeny, C_{2-4}alkynyl, phenyl or heterocyclic group (on a ring carbon) may be optionally substituted by one or more R^6 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8.

More particularly R^5 is methyl, ethyl, ethenyl and ethynyl, a heterocyclic group {wherein if the heterocyclic group contains an -NH- moiety then that nitrogen may be optionally substituted with methyl, acetyl or mesyl} optionally substituted on a ring carbon by one or more methyl, halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, *N*-methylpiperazinyl, *N*-acetylpiperazinyl, *N*-mesylpiperazinyl, amino, methanesulphinyl, acetamido, methanesulphonyl and phenyl optionally substituted by one or more methyl, halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, *N*-methylpiperazinyl, *N*-acetylpiperazinyl, *N*-mesylpiperazinyl, amino, methanesulphinyl, acetamido, methanesulphonyl.

In a further aspect of the invention R^5 is 4-mesylphenyl, 4-methylthiophenyl, 4-fluorophenyl or 4-cyanophenyl.

Preferably E is -O-, -N(R^9)-, -C(O)-, -N(R^9)C(O)-, -C(O)N(R^9)-, -S(O)$_a$- wherein a is 1 or 2, -OC(O)-, -C(O)O-, -N(R^9)C(O)O-, -OC(O)N(R^9)-, -SO_2N(R^9)-, -N(R^9)SO_2-, -N(R^9)C(O)N(R^9)-, -SO_2NHC(O)-, -SO_2N(R^9)C(O)- or -C(O)NHSO_2- or E is a direct bond.

More preferably E is -O-, -N(R^9)-, -C(O)-, -N(R^9)C(O)-, -C(O)N(R^9)-, -S(O)$_a$- wherein a is 1 or 2, -SO_2N(R^9)-, -N(R^9)SO_2- or -N(R^9)C(O)N(R^9)- or E is a direct bond.

Particularly E is $-N(R^9)C(O)-$, $-C(O)N(R^9)-$, $-S(O)_a-$ wherein a is 1 or 2, $-SO_2N(R^9)-$, $-N(R^9)SO_2-$ or $-N(R^9)C(O)N(R^9)-$ or E is a direct bond.

In another aspect of the invention E is $-SO_2-$, -S-, -C(O)- or -C(O)NH-.

Preferably R^6 is C_{1-6}alkyl, halo, hydroxy, amino, carboxy, C_{1-6}alkylsulphonyl, C_{1-6}alkylsulphonylamino, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl or a heterocyclic group wherein in R^6 any C_{1-6}alkyl group may be optionally substituted by one or more R^7 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8.

More preferably R^6 is C_{1-4}alkyl, halo, hydroxy, amino, carboxy, C_{1-4}alkylsulphonyl, C_{1-4}alkylsulphonylamino, *N*-(C_{1-4}alkyl)aminosulphonyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl or a heterocyclic group wherein in R^6 any C_{1-4}alkyl group may be optionally substituted by one or more R^7 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8.

Particularly R^6 is methyl, ethyl, 2-hydroxyethylamino, halo, hydroxy, amino, carboxy, mesyl, ethylsulphonyl, mesylamino, ethylsulphonylamino, *N*-methylaminosulphonyl, *N*-ethylaminosulphonyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl or a heterocyclic group wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from mesyl, methyl or acetyl.

Preferably R^7 is C_{1-6}alkyl, halo, hydroxy, amino, carboxy, C_{1-6}alkylsulphonyl, C_{1-6}alkylsulphonylamino, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl or a heterocyclic group wherein in R^7 any C_{1-6}alkyl group may be optionally substituted by one or more R^{12}.

More preferably R^7 is C_{1-4}alkyl, halo, hydroxy, amino, carboxy, C_{1-4}alkylsulphonyl, C_{1-4}alkylsulphonylamino, *N*-(C_{1-4}alkyl)aminosulphonyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl or a heterocyclic group wherein in R^7 any C_{1-4}alkyl group may be optionally substituted by one or more R^{12}.

Particularly R^7 is methyl, ethyl, 2-hydroxyethyl, halo, hydroxy, amino, carboxy, mesyl, ethylsulphonyl, mesylamino, ethylsulphonylamino, *N*-methylaminosulphonyl, *N*-ethylaminosulphonyl, *N*-(C_{1-4}alkyl)$_2$carbamoyl or a heterocyclic group.

Preferably R^8 is C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl or *N,N*-(C_{1-6}alkyl)$_2$carbamoyl.

More preferably R^8 is C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl or *N,N*-(C_{1-4}alkyl)$_2$carbamoyl.

More preferably R^8 is methyl, ethyl, acetyl, mesyl, ethylsulphonyl, carbamoyl, *N*-methylcarbamoyl or *N,N*-dimethylcarbamoyl.

Preferably R^9 is hydrogen or C_{1-4}alkyl optionally substituted by one or more R^{10} with the proviso that R^{10} is not a substituent on the carbon attached to a nitrogen atom.

More preferably R^9 is hydrogen, methyl or ethyl optionally substituted by one or more R^{10} with the proviso that R^{10} is not a substituent on the carbon attached to a nitrogen atom.

Particularly R^9 is hydrogen.

In another aspect of the invention particularly R^9 is methyl.

Preferably R^{10} is hydroxy.

Preferably R^{11} is C_{1-6}alkyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl.

More preferably R^{11} is C_{1-4}alkyl, C_{1-4}alkanoyl or C_{1-4}alkylsulphonyl.

Particularly R^{11} is methyl, mesyl or acetyl.

Particularly R^{12} is hydroxy.

Particularly R^{13} is hydroxy.

In one aspect of the invention preferably n is 0.

In another aspect of the invention preferably n is 1.

In an additional aspect of the invention preferably n is 2.

In a further aspect of the invention preferably n is 3.

In a further additional aspect of the invention preferably n is 4.

Preferably n is 1-3.

More preferably n is 2 or 3.

In another aspect of the invention, preferably n is 0-3.

Preferably R^3 is phenylsulphonyl optionally substituted by R^6, phenylthio optionally substituted by R^6, phenylcarbonyl optionally substituted by R^6 or C_{1-4}alkyl optionally substituted by R^6.

More preferably R^3 is 4-mesylphenylsulphonyl, 4-methylthiophenylthio, 4-fluorophenylcarbonyl or methyl.

In another aspect of the invention preferably R^3 is selected from amino, methyl, 4-mesylphenylsulphonyl, 4-methylthiophenylthio, 4-fluorobenzoyl and 4-cyanobenzoylamino.

Where -C(OH)(R^1)(R^2) represents a chiral center, the R-configuration is generally the preferred stereochemistry.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** (as depicted above) wherein:

Ring A is piperidyl, piperazinyl or indolinyl; wherein said piperazinyl is optionally substituted on nitrogen by R^4-D-;

One of R^1 and R^2 is methyl and the other is trifluoromethyl;

R^3 is a substituent on carbon and is selected from amino, methyl, 4-mesylphenylsulphonyl, 4-methylthiophenylthio, 4-fluorobenzoyl and 4-cyanobenzoylamino;

R^4 is C_{1-4}alkyl, phenyl {optionally substituted with one or more *t*-butyl, isopropyl, nitro, halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, cyano, acetyl, methoxy or carboxy} or thienyl;

D is -SO_2- or -C(O)-; and

n is 0 to 3;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in an additional aspect of the invention there is provided a compound of formula **(I)** (as depicted above) wherein:

Ring A is piperazinyl; wherein said piperazinyl is substituted on nitrogen by R^4-D-;

One of R^1 and R^2 is methyl and the other is trifluoromethyl;

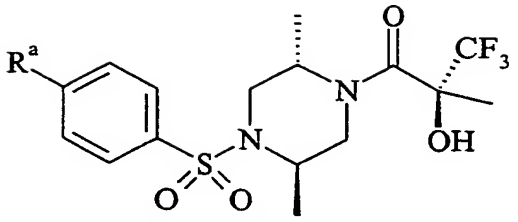
R^3 is a substituent on carbon and is methyl;

R^4-D- is 4-carboxyphenylsulphonyl, 4-(*N,N*-dimethylcarbamoyl)phenylsulphonyl, 4-fluorophenylsulphonyl, 4-(2-hydroxyethylamino)phenylsulphonyl, 4-cyanophenylsulphonyl or 4-methoxyphenylsulphonyl;

n is 2;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further aspect of the invention there is provided a compound of formula **(I')**:



(I')

wherein:

R^a is carboxy, *N,N*-dimethylcarbamoyl, fluoro, 2-hydroxyethylamino, cyano or methoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

A preferred compound of the invention is any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred compounds of the invention are Examples 4, 5, 6, 11, 12 and 15 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred aspects of the invention are those which relate to the compound or a pharmaceutically acceptable salt thereof.

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which elevates PDH activity and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated by those skilled in the art that certain compounds of formula (I) contain one or more asymmetrically substituted carbon and/or sulphur atoms, and accordingly may exist in, and be isolated as enantiomerically pure, a mixture of diastereoisomers or as a racemate. It will also be appreciated by those skilled in the art that certain compounds of formula (I) contain substituents on a saturated heterocycle that may bear a *syn-* or *anti-* (or *cis-* and *trans*) relationship. It is to be understood that the present invention encompasses all such geometric isomers. Some compounds may exhibit polymorphism. It is to be understood

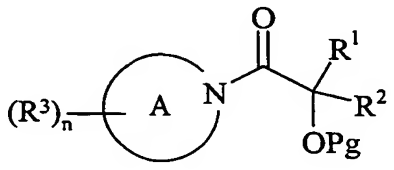
that the present invention encompasses any racemic, optically-active, enantiomerically pure, mixture of diastereoisomers, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the elevation of PDH activity, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, (for example WO 9738124), by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the elevation of PDH activity by the standard tests described hereinafter.

It is also to be understood that certain compounds of the formula (I) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which elevate PDH activity.

A compound of the formula (I), or salt thereof, and other compounds of the invention (as hereinafter defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in European Patent Applications, Publication Nos. 0524781, 0617010, 0625516, and in GB 2278054, WO 9323358 and WO 9738124.

Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process (in which variable groups are as defined for formula (I) unless otherwise stated) comprises of:

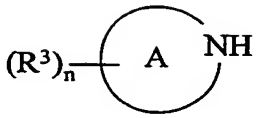
(a) deprotecting a protected compound of formula (II):



(II)

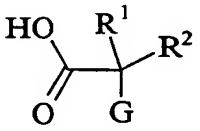
where Pg is an alcohol protecting group;

(b) coupling an amine of formula (III):



(III)

with an acid of formula (IV):



(IV)

wherein G is a hydroxyl group;

(c) coupling an amine of formula (III) with an activated acid derivative of formula (IV) wherein G is a hydroxyl group which may be protected as an ester or ether;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

Suitable values for Pg are a benzyl group, a silyl group or an acetyl protecting group.

Specific conditions of the above reactions are as follows:

Process a)

Suitable reagents for deprotecting an alcohol of formula (II) are for example:

1) when Pg is benzyl:

(i) hydrogen in the presence of palladium/carbon catalyst, i.e. hydrogenolysis; or

(ii) hydrogen bromide or hydrogen iodide;

2) when Pg is a silyl protecting group:

(i) tetrabutylammonium fluoride; or

(ii) aqueous hydrofluoric acid;

3) when Pg is acetyl:

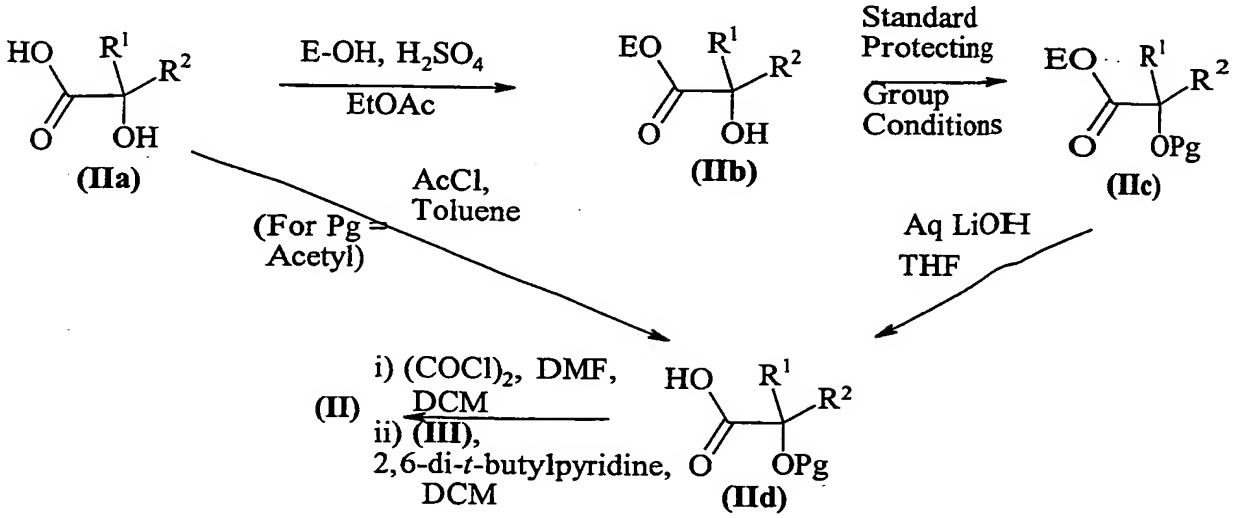
i) mild aqueous base for example lithium hydroxide; or

ii) ammonia or an amine such as dimethylamine.

The reaction can be conducted in a suitable solvent such as ethanol, methanol, acetonitrile, or dimethylsulphoxide and may conveniently be performed at a temperature in

the range of -40 to 100°C.

Compounds of formula **(II)** may be prepared according to the following scheme:



Scheme 1

E is a carboxy protecting group. Suitable values for E include C_{1-6}alkyl, such as methyl and ethyl.

Compounds of formula **(IIa)** and **(III)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process b)

An amine of formula **(III)** and an acid of formula **(IV)** may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, for example conditions such as those described above for the coupling of **(IId)** and **(III)**, or carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran, and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Compounds of formula **(IV)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

If the resolved acid of formula **(IV)** is required it may be prepared by any of the

known methods for preparation of optically-active forms (for example, by recrystallization of the chiral salt {for example WO 9738124}, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase). For example if an (R)-(+) resolved acid is required it may be prepared by the method of Scheme 2 in World Patent Application Publication No. WO 9738124 for preparation of the (S)-(-) acid, i.e. using the classical resolution method described in European Patent Application Publication No. EP 0524781, also for preparation of the (S)-(-) acid, except that (1S,2R)-norephedrine may be used in place of (S)-(-)-1-phenylethylamine. The chiral acid may also be prepared by using the enzymatic resolution method as described in Tetrahedron Asymmetry, 1999, 10, 679.

Process c)

An amine of formula **(III)** may be coupled with an activated acid derivative of formula **(IV)** for example acid chlorides, acid anhydrides, or phenyl esters, wherein G is a hydroxyl group which may be suitably protected as a stable ester or ether. This coupling may be achieved optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran, and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C;

If not commercially available, the necessary starting materials for the procedures such as that described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples.

For example, it will be appreciated that certain of the optional aromatic substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications or interconversions either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular

examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acylhalide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by, for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl using, for example, hydrogen peroxide in acetic acid with heating or 3-chloroperbenzoic acid. Particular examples of functional group interconversions are for example conversion of an aniline into a halophenyl by, for example, diazotisation in the presence of cupurous halides.

It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as, for example hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an

arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

In cases where compounds of formula (I) are sufficiently basic or acidic to form stable acid or basic salts, administration of the compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following. Examples of suitable pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiologically acceptable anion, for example, tosylate, methanesulphonate, acetate, tartrate, citrate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed such as sulphate, nitrate, and hydrochloride.

Pharmaceutically acceptable salts may be obtained using standard procedures well

known in the art, for example by reacting a sufficiently basic compound of formula (I) (or its ester) with a suitable acid affording a physiologically acceptable anion. It is also possible with most compounds of the invention to make a corresponding alkali metal (e.g. sodium, potassium, or lithium) or alkaline earth metal (e.g. calcium) salt by treating a compound of formula (I) (and in some cases the ester) with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (e.g. the ethoxide or methoxide) in aqueous medium followed by conventional purification techniques.

The compounds of the formula (I) may be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the formula (I). Examples of prodrugs include *in vivo* hydrolysable esters of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable *in vivo* hydrolysable esters for a compound of the formula (I) containing a carboxy group include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable *in vivo* hydrolysable esters of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. Other *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents for benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

In vivo cleavable prodrugs of compounds of formula (I) also include *in vivo*

hydrolysable amides of compounds of the formula (I) containing a carboxy group, for example, a *N*-C_{1-6}alkyl or *N*-di-C_{1-6}alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N*-dimethyl, *N*-ethyl-*N*-methyl or *N*-diethyl amide.

The identification of compounds which elevate PDH activity is the subject of the present invention. These properties may be assessed, for example, using one or more of the procedures set out below:

In vitro elevation of PDH activity

This assay determines the ability of a test compound to elevate PDH activity. cDNA encoding PDH kinase may be obtained by Polymerase Chain Reaction (PCR) and subsequent cloning. This may be expressed in a suitable expression system to obtain polypeptide with PDH kinase activity. For example rat PDHkinaseII (rPDHKII) obtained by expression of recombinant protein in Escherichia coli (E. Coli), was found to display PDH kinase activity.

In the case of the rPDHKII (Genbank accession number U10357) a 1.3kb fragment encoding the protein was isolated by PCR from rat liver cDNA and cloned into a vector (for example pQE32 - Quiagen Ltd.). The recombinant construct was transformed into E. coli (for example M15pRep4 - Quiagen Ltd.). Recombinant clones were identified, plasmid DNA was isolated and subjected to DNA sequence analysis. One clone which had the expected nucleic acid sequence was selected for the expression work. Details of the methods for the assembly of recombinant DNA molecules and the expression of recombinant proteins in bacterial systems can be found in standard texts for example Sambrook et al, 1989, Molecular Cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press. Other known PDH kinases for use in assays, may be cloned and expressed in a similar manner.

For expression of rPDHKII activity, E. coli strain M15pRep4 cells were transformed with the pQE32 vector containing rPDHKII cDNA. This vector incorporates a 6-His tag onto the protein at its N-terminus. E. coli were grown to an optical density of 0.6 (600 nM) and protein expression was induced by the addition of 10 μM isopropylthio-β-galactosidase. Cells were grown for 18 hours at 18°C and harvested by centrifugation. The resuspended cell paste was lysed by homogenisation and insoluble material removed by centrifugation at 24000xg for 1 hour. The 6-His tagged protein was removed from the supernatant using a nickel chelating nitrilotriacetic acid resin (Ni-NTA: Quiagen Ltd.) matrix (Quiagen) which was washed with 20 mM tris(hydroxymethyl)aminomethane-hydrogen chloride, 20 mM

imidazole, 0.5 M sodium chloride pH 8.0, prior to elution of bound protein using a buffer containing 20 mM tris(hydroxymethyl)aminomethane-hydrogen chloride, 200 mM imidazole, 0.15 M sodium chloride pH 8.0. Eluted fractions containing 6-His protein were pooled and stored in aliquots at -80°C in 10% glycerol.

Each new batch of stock enzyme was titrated in the assay to determine a concentration giving approximately 90% inhibition of PDH in the conditions of the assay. For a typical batch, stock enzyme was diluted to 7.5μg/ml.

For assay of the activity of novel compounds, compounds were diluted with 10% dimethylsulphoxide (DMSO) and 10μl transferred to individual wells of 96-well assay plates. Control wells contained 20μl 10% DMSO instead of compound. 40μl Buffer containing 50mM potassium phosphate buffer pH 7.0, 10mM ethylene glycol-bis(β-aminoethyl ether)-N,N-tetracetic acid (EGTA), 1mM benzamidine, 1mM phenylmethylsulphonyl fluoride (PMSF), 0.3mM tosyl-L-lysine chloromethyl ketone (TLCK), 2mM dithiothreitol (DTT), recombinant rPDHKII and compounds were incubated in the presence of PDH kinase at room temperature for 45 minutes. In order to determine the maximum rate of the PDH reaction a second series of control wells were included containing 10% DMSO instead of compound and omitting rPDHKII. PDH kinase activity was then initiated by the addition of 5 μM ATP, 2 mM magnesium chloride and 0.04 U/ml PDH (porcine heart PDH Sigma P7032) in a total volume of 50 μl and plates incubated at ambient temperature for a further 45 minutes. The residual activity of the PDH was then determined by the addition of substrates (2.5mM coenzyme A, 2.5mM thiamine pyrophosphate (cocarboxylase), 2.5mM sodium pyruvate, 6mM NAD in a total volume of 80μl and the plates incubated for 90 minutes at ambient temperature. The production of reduced NAD (NADH) was established by measured optical density at 340nm using a plate reading spectrophotometer. The ED_{50} for a test compound was determined in the usual way using results from 12 concentrations of the compound.

(b) *In vitro* elevation of PDH activity in isolated primary cells

This assay determines the ability of compounds to stimulate pyruvate oxidation in primary rat hepatocytes.

Hepatocytes were isolated by the two-step collagenase digestion procedure described by Seglen (Methods Cell Biol. (1976) 13, 29-33) and plated out in 6-well culture plates (Falcon Primaria) at 600000 viable cells per well in Dulbecco's Modified Eagles Medium

(DMEM, Gibco BRL) containing 10% foetal calf serum (FCS), 10% penicillin/streptomycin (Gibco BRL) and 10% non-essential amino acids (NEAA, Gibco BRL). After 4 hours incubation at 37°C in 5% CO_2, the medium was replaced with Minimum Essential Medium (MEM, Gibco BRL) containing NEAA and penicillin/streptomycin as above in addition to 10nM dexamethasone and 10nM insulin.

The following day cells were washed with phosphate buffered saline (PBS) and medium replaced with 1ml HEPES-buffered Krebs solution (25mM HEPES, 0.15M sodium chloride, 25 mM sodium hydrogen carbonate, 5mM potassium chloride, 2mM calcium chloride, 1mM magnesium sulphate, 1 mM potassium dihydrogen phosphate) containing the compound to be tested at the required concentration in 0.1% DMSO. Control wells contained 0.1% DMSO only and a maximum response was determined using a 10 μM treatment of a known active compound. After a preincubation period of 40 minutes at 37°C in 5% CO_2, cells were pulsed with sodium pyruvate to a final concentration of 0.5mM (containing 1-^{14}C sodium pyruvate (Amersham product CFA85) 0.18Ci/mmole) for 12 minutes. The medium was then removed and transferred to a tube which was immediately sealed with a bung containing a suspended centre well. Absorbent within the centre well was saturated with 50% phenylethylamine, and CO_2 in the medium released by the addition of 0.2μl 60% (w/v) perchloric acid (PCA). Released $^{14}CO_2$ trapped in the absorbent was determined by liquid scintillation counting. The ED_{50} for a test compound was determined in the usual way using results from 7 concentrations of the compound.

(c) *In vivo* elevation of PDH activity

The capacity of compounds to increase the activity of PDH in relevant tissues of rats may be measured using the test described hereinafter. Typically an increase in the proportion of PDH in its active, nonphosphorylated form may be detected in muscle, heart, liver and adipose tissue after a single administration of an active compound. This may be expected to lead to a decrease in blood glucose after repeated administration of the compound. For example a single administration of DCA, a compound known to activate PDH by inhibition of PDH kinase (Whitehouse, Cooper and Randle (1974) Biochem. J. 141, 761-774) 150 mg/kg, intraperitoneally, increased the proportion of PDH in its active form (Vary et al. (1988) Circ. Shock 24, 3-18) and after repeated administration resulted in a significant decrease in plasma glucose (Evans and Stacpoole (1982) Biochem. Pharmacol.31, 1295-1300).

Groups of rats (weight range 140-180 g) are treated with a single dose or multiple doses of the compound of interest by oral gavage in an appropriate vehicle. A control group of rats is treated with vehicle only. At a fixed time after the final administration of compound, animals are terminally anaesthetised, tissues are removed and frozen in liquid nitrogen. For determination of PDH activity, muscle samples are disrupted under liquid nitrogen prior to homogenisation by one thirty-second burst in a Polytron homogenizer in 4 volumes of a buffer containing 40 mM potassium phosphate pH 7.0, 5 mM EDTA, 2mM DTT, 1% Triton X-100, 10mM sodium pyruvate, 10μM phenylmethylsulphonyl chloride (PMSF) and2μg/ml each of leupeptin, pepstain A and aprotinin. Extracts are centrifuged before assay. A portion of the extract is treated with PDH phosphatase prepared from pig hearts by the method of Siess and Wieland (Eur. J. Biochem (1972) 26, 96): 20 μl extract, 40 μl phosphatase (1:20 dilution), in a final volume of 125 μl containing 25 mM magnesium chloride, 1 mM calcium chloride. The activity of the untreated sample is compared with the activity of the dephosphorylated extract thus prepared. PDH activity is assayed by the method of Stansbie et al., (Biochem. J. (1976) 154, 225). 50 μl Extract is incubated with 0.75 mM NAD, 0.2 mM CoA, 1.5 mM thiamine pyrophosphate (TPP) and 1.5mM sodium pyruvate in the presence of 20 μg/ml p-(p-amino-phenylazo) benzene sulphonic acid (AABS) and 50 mU/ml arylamine transferase (AAT) in a buffer containing 100 mM tris(hydroxymethyl)aminomethane, 0.5 mM EDTA, 50mM sodium fluoride, 5mM 2-mercaptoethanol and 1mM magnesium chloride pH 7.8. AAT is prepared from pigeon livers by the method of Tabor et al. (J. Biol. Chem. (1953) 204, 127). The rate of acetyl CoA formation is determined by the rate of reduction of AABS which is indicated by a decrease in optical density at 460 nm.

Liver samples are prepared by an essentially similar method, except that sodium pyruvate is excluded from the extraction buffer and added to the phosphatase incubation to a final concentration of 5mM.

Treatment of an animal with an active compound results in an increase in the activity of PDH complex in tissues. This is indicated by an increase in the amount of active PDH (determined by the activity of untreated extract as a percentage of the total PDH activity in the same extract after treatment with phosphatase).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I) as defined hereinbefore or a

pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) for example as a sterile solution, suspension or emulsion, for topical administration for example as an ointment or cream or for rectal administration for example as a suppository. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square metre body area of the animal, i.e. approximately 0.1-100 mg/kg. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient.

According to a further aspect of the present invention there is provided a compound of the formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention elevate PDH activity and are therefore of interest for their blood glucose-lowering effects.

A further feature of the present invention is a compound of formula (I) and pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof for use as a medicament.

Conveniently this is a compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use as a medicament for producing an elevation of PDH activity in a warm-blooded animal such as a human being.

Particularly this is a compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use as a medicament for treating diabetes mellitus in a warm-blooded animal such as a human being.

In another aspect of the invention, particularly this is a compound of formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use as a

medicament for treating diabetes mellitus, peripheral vascular disease and myocardial ischaemia in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the production of an elevation of PDH activity in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the treatment of diabetes mellitus in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the treatment of diabetes mellitus, peripheral vascular disease and myocardial ischaemia in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an elevation of PDH activity in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating diabetes mellitus in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating diabetes mellitus, peripheral vascular disease and myocardial ischaemia in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The elevation of PDH activity described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. For example in the treatment of diabetes mellitus chemotherapy may include the following main categories of treatment:

i) insulin;

ii) insulin secretagogue agents designed to stimulate insulin secretion (for example glibenclamide, tolbutamide, other sulphonylureas);

iii) oral hypoglycaemic agents such as metformin, thiazolidinediones;

iv) agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

v) agents designed to treat complications of prolonged hyperglycaemia;

vi) other agents used to treat lactic acidaemia;

vii) inhibitors of fatty acid oxidation;

viii) lipid lowering agents;

ix) agents used to treat coronary heart disease and peripheral vascular disease such as aspirin, pentoxifylline, cilostazol; and/or

x) thiamine.

As stated above the compounds defined in the present invention are of interest for their ability to elevate the activity of PDH. Such compounds of the invention may therefore be useful in a range of disease states including diabetes mellitus, peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, myocardial ischaemia, cerebral ischaemia and reperfusion, muscle weakness,

hyperlipidaemias, Alzheimers disease and/or atherosclerosis. Alternatively such compounds of the invention may be useful in a range of disease states including peripheral vascular disease, (including intermittent claudication), cardiac failure and certain cardiac myopathies, myocardial ischaemia, cerebral ischaemia and reperfusion, muscle weakness, hyperlipidaemias, Alzheimers disease and/or atherosclerosis in particular peripheral vascular disease and myocardial ischaemia.

In addition to their use in therapeutic medicine, the compounds of formula (I) and pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of elevators of PDH activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10 g or 20 g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio chloroform ($CDCl_3$) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the negative mass ion - $(M-H)^-$; and

(x) the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane; and
EtOAc	ethyl acetate;

(xi) where (R) or (S) stereochemistry is quoted at the beginning of a name, unless further clarified, it is to be understood that the indicated stereochemistry refers to the $-C(O)-C^*(OH)(R^1)(R^2)$ centre as depicted in formula (I) (where C* is the chiral carbon); and

(xii) where a Biotage cartridge is referred to this means a cartridge containing KP-SIL™ silica, 60Å particle size 32-63μM, supplied by Biotage, a division of Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

Example 1

(R)-[4-(4-Fluorobenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperidine]

A solution of (S)-3,3,3-trifluoro-2-trimethylsilyoxy-2-methylpropanoyl chloride (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (293 mg, 1.2 mmol) in EtOAc (5 ml) was added to a stirred mixture of 4-(4-fluorobenzoyl)piperidine (207 mg, 1.0 mmol) and triethylamine (0.21 ml, 1.5 mmol) in EtOAc (25 ml). The resultant mixture was stirred at ambient temperature for 2 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was dissolved in methanol (10 ml), treated with 1 M hydrochloric acid (2 ml) and the mixture stirred at ambient temperature for 1 hour. The methanol was evaporated, the aqueous layer was extracted with EtOAc (2 x 25 ml), the EtOAc extracts were washed with saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was chromatographed on silica with 10% EtOAc / DCM as

eluent to give a solid which was recrystallized from EtOAc / hexane to give the title compound as a solid (104 mg, 0.3 mmol). Mp: 78-79°C; NMR: 1.7 (s, 3H), 1.8-2.0 (m, 4H), 3.2 (dd, 2H), 3.5 (m, 1H), 4.4 (dd, 2H), 5.25 (s, 1H), 7.15 (dd, 2H), 8.0 (dd, 2H); m/z 346.

Example 2

(R)-[(2S,5R)-2-Methyl-5-methyl-4-ethanesulphonyl-1-(3,3,3-trifluoro-2-hydroxy-2-methyl-propionyl)piperazine]

A solution of ethane sulphonyl chloride (91 mg, 0.707 mmol) in EtOAc (10 ml) was added to a stirred mixture of (R)-[(2S,5R)-2-methyl-5-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (150 mg, 0.59 mmol) and triethylamine (0.125 ml, 0.886 mmol) in EtOAc (15 ml). The resultant mixture was stirred at ambient temperature for 4 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was recrystallized from EtOAc / hexane to give the title compound as a solid (97 mg, 0.28 mmol). Mp: 142-144°C; NMR: 1.15 (d, 3H), 1.3 (m, 6H), 1.65 (s, 3H), 2.9 (m, 2H), 3.3 (s, 1H), 3.35 (q, 2H), 4.05 (s, 1H) , 4.15 (s, 1H), 4.4 (s, 1H), 4.7 (s, 1H); m/z 345.

Example 3

(R)-[(2S,5R)-2-Methyl-5-methyl-4-(thien-2-ylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

A solution of 2-thiophene sulphonyl chloride (129 mg, 0.707 mmol) in EtOAc (10 ml) was added to a stirred mixture of (R)-[(2S,5R)-2-methyl-5-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (150 mg, 0.59 mmol) and triethylamine (0.125 ml, 0.886 mmol) in EtOAc (15 ml). The resultant mixture was stirred at ambient temperature for 4 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was recrystallized from EtOAc / hexane to give the title compound as a solid (71 mg, 0.18 mmol). Mp: 116-117°C; NMR: 0.95 (d, 3H), 1.25 (dd, 3H), 1.65 (s, 3H), 3.2 (dd, 1H), 3.3 (s, 1H), 3.5 (dd, 1H), 4.05 (s, 1H) , 4.15 (s, 1H), 4.3 (s, 1H), 4.75 (s, 1H), 7.0 (dd, 1H), 7.5 (dd, 2H); m/z 399.

Example 4

(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-carboxyphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

A solution of 4-chlorosulphonyl benzoic acid (265 mg, 1.2 mmol) in EtOAc (10 ml) was added to a stirred mixture of (R)-[(2S,5R)-2-methyl-5-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (254 mg, 1.0 mmol) and triethylamine (0.31 ml, 2.2 mmol) in EtOAc (15 ml). The resultant mixture was stirred at ambient temperature for 2 hours, washed with 1 M hydrochloric acid, brine, dried and evaporated. The residue was recrystallized from EtOAc / hexane to give the title compound as a solid (410 mg, 0.936 mmol). Mp: 194-196°C; NMR: 0.9 (d, 3H), 1.2 (dd, 3H), 1.55 (s, 3H), 3.0 (dd, 1H), 3.15 (dd, 1H), 3.4 (s, 1H), 4.1 (m, 2H) , 4.6 (s, 1H), 5.15 (s, 1H), 7.75 (d, 2H), 8.05 (d, 2H); m/z 437.

Example 5

(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-dimethylcarbamoylphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

Oxalyl chloride (0.08 ml, 0.88 mmol) was added to a solution of (R)-[(2S,5R)-2-methyl-5-methyl-4-(4-carboxyphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (320 mg, 0.73 mmol) (Example 4) in DCM (25 ml). The resultant mixture was stirred at ambient temperature for 4 hours, evaporated to dryness, the residue treated with 40% aqueous dimethylamine (0.82 ml, 7.3 mmol) and the resultant mixture was stirred at ambient temperature overnight. The mixture was treated with EtOAc (25 ml), washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was chromatographed on silica with 50% EtOAc in DCM as eluent to give a solid which was recrystallized from EtOAc / hexane to give the title compound as a solid (26 mg, 0.056 mmol). Mp: 86-87°C; NMR: 0.95 (d, 3H), 1.25 (dd, 3H), 1.65 (s, 3H), 2.95 (s, 3H), 3.1 (s, 3H), 3.25 (dd, 1H), 3.35 (dd, 1H), 3.5 (dd, 1H), 4.2 (m, 2H) , 4.5 (s, 1H), 4.8 (s, 1H), 7.5 (d, 2H), 7.85 (d, 2H); m/z: 464.

Example 6

(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-fluorophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

A solution of 4-fluorobenzene sulphonyl chloride (234 mg, 1.2 mmol) in EtOAc (10 ml) was added to a stirred mixture of (R)-[(2S,5R)-2-methyl-5-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (254 mg, 1.0 mmol) and triethylamine (0.17 ml, 1.2 mmol) in EtOAc (15 ml). The resultant mixture was stirred at ambient temperature for 2 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was recrystallized from EtOAc / hexane to give the title compound as a solid (230 mg, 0.56 mmol). Mp: 174-175°C; NMR: 0.95 (d, 3H), 1.25 (d, 3H), 1.75 (s, 3H), 3.25 (dd, 1H), 3.35 (d, 1H), 3.5 (dd, 1H), 4.15 (m, 2H), 4.3 (s, 1H), 4.75 (s, 1H), 7.2 (d, 2H), 7.8 (d, 2H); m/z 411.

Example 7

(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-fluorobenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

A solution of 4-fluorobenzoyl chloride (190 mg, 1.2 mmol) in EtOAc (10 ml) was added to a stirred mixture of (R)-[(2S,5R)-2-methyl-5-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (254 mg, 1.0 mmol) and triethylamine (0.17 ml, 1.2 mmol) in EtOAc (15 ml). The resultant mixture was stirred at ambient temperature for 2 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was chromatographed on silica with 20% EtOAc in DCM as eluent to give the title compound as a solid which was recrystallized from EtOAc / hexane (290 mg, 0.77 mmol). Mp: 177-178°C; NMR: 1.25 (d, 6H), 1.75 (s, 3H), 3.4 (m, 3H), 4.0 (m, 1H), 4.2 (m, 1H), 4.5 (s, 1H), 4.75 (s, 1H), 7.2 (d, 2H), 7.8 (d, 2H); m/z: 375.

Example 8

(R)-[5-(4-Methylsulphanylphenylsulphanyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)indoline]

Oxalyl chloride (0.35 ml, 4.0 mmol) was added to a stirred suspension of (R)-(+)-2-hydroxy-2-methyl-3,3,3-trifluoropropanoic acid (0.58 g, 3.7 mmol) (Method A) in DCM (10 ml) containing DMF (1 drop). The mixture was stirred at ambient temperature for 18 hours and was then added to a solution of 5-(4-methylsulphanylphenylsulphanyl) indoline (1.03 g) (Method B) and 2,6-diphenylpyridine (0.84 g, 3.64 mmol) in DCM (20 ml). The mixture was stirred for 16 hours, volatile material was removed by evaporation, and the residue was purified by flash column chromatography on silica gel eluting with 10-20% EtOAc / *iso*-hexane to give the title compound (0.935 g, 2.3 mmol) as a solid. NMR: 1.80 (s, 3H), 2.50 (s, 3H), 3.11-3.19 (m, 2H), 4.19-4.29 (m, 1H), 4.38-4.47 (m, 1H), 4.86 (s, 1H), 7.19-7.27 (m, 6H), 8.20 (d, 1H); m/z (+ve ESP): 414 $(M+H)^+$.

Example 9

(R)-[5-(4-Mesylphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)indoline]

Hydrogen peroxide (5 ml of a 30 wt. % solution in water) was added to a solution of (R)-[5-(4-methylsulphanylphenylsulphanyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methyl-propionyl)indoline] (0.53 g, 1.3 mmol) (Example 8) in glacial acetic acid (10 ml) and the mixture was heated at 95°C for 1 hour. The reaction mixture was allowed to cool to room temperature, EtOAc (150 ml) was added and the mixture was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 150 ml) and brine (150 ml) and dried. Volatile material was removed by evaporation and the residue was purified on a silica gel Mega Bond Elut column eluting with 0-60% EtOAc / *iso*-hexane to give the title compound (0.42 g, 0.88 mmol) as a white solid. NMR (DMSO): 1.61 (s, 3H), 3.16-3.22 (m, 2H), 3.29 (s, 3H), 4.34-4.55 (m, 2H), 7.33 (s, 1H), 7.86-7.90 (m, 2H), 8.12-8.25 (m, 5H); m/z 476.

Example 10

(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-dimethylcarbamoylbenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

To a stirred solution of (R)-[(2S,5R)-2-methyl-5-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (400 mg, 1.57 mmol) and triethylamine (0.4 ml, 2.84 mmol) in EtOAc (25 ml) was added a solution of 4-dimethylcarbamoylbenzoyl chloride (350 mg, 1.66 mmol) in EtOAc (25 ml). The resultant

mixture was stirred at ambient temperature for 24 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was chromatographed on silica with EtOAc as eluent to give the title compound as a solid (120 mg, 0.28 mmol). NMR: 1.1-1.3 (m, 6H), 1.6 (s, 3H), 2.9 (s, 3H), 3.1 (s, 3H), 3.25 (m, 1H), 3.4 (m, 1H), 4.25 (s, 2H), 4.65 (s, 1H), 4.9 (s, 1H), 5.2 (s, 1H), 7.3-7.4 (dd, 4H); m/z 428.

Example 11

(R)-{(2S,5R)-2-Methyl-5-methyl-4-[4-(2-hydroxyethylamino)phenylsulphonyl]-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine}

To a solution of (R)-[(2S,5R)-2-methyl-5-methyl-4-(4-fluorophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (Example 6, 350 mg, 0.85 mmol) in 1-methyl-2-pyrrolidone (2 ml) was added ethanolamine (114 mg, 1.87 mmol) and the mixture heated at 120°C for 24 hours. The mixture was cooled to ambient temperature, poured onto saturated ammonium chloride solution (30 ml), the mixture extracted with diethyl ether (2 x 30 ml), the combined ether extracts washed with brine, dried and evaporated. The residue was chromatographed on silica with EtOAc as eluent to give the title compound as a solid (143 mg, 0.32 mmol). NMR: 0.95 (d, 3H), 1.55 (d, 3H), 1.6 (s, 3H), 3.1 (m, 2H), 3.3 (dt, 2H), 3.4 (d, 1H), 3.8 (dt, 2H), 4.2 (s, 1H), 4.6 (m, 2H), 6.6 (d, 2H), 7.5 (d, 2H); m/z 411.

Example 12

(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-cyanophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

To a stirred solution of (R)-[(2S,5R)-2-methyl-5-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (*J. Med. Chem.*, **1999**, *42*, 2741-2746) (254 mg, 1.0 mmol) and triethylamine (0.17 ml, 1.2 mmol) in EtOAc (15 ml) was added a solution of 4-cyanobenzene sulphonyl chloride (220 mg, 1.1 mmol) in EtOAc (10 ml). The resultant mixture was stirred at ambient temperature for 2 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was recrystallized from EtOAc / hexane to give the title compound as a solid (280 mg, 0.56 mmol). Mp: 186-187°C; NMR: 0.95 (d, 3H), 1.25 (d, 3H), 1.75 (s, 3H), 3.25 (dd, 1H), 3.35 (d, 1H), 3.5 (dd, 1H), 4.2 (m, 3H), 4.75 (s, 1H), 7.8 (d, 2H), 7.9 (d, 2H); m/z 418.

Examples 13-19

The procedure described in Example 12 was repeated using the appropriate acid chloride or sulphonyl chloride to replace the 4-cyanobenzene sulphonyl chloride to obtain the compounds described below.

No	Example	m/z
13	(R)-[(2S,5R)-2-Methyl-5-methyl-4-(2-chloro-4-cyanophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]	452
14	(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-acetylphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]	435
15	(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-methoxyphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]	423
16	(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-bromophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]	471
17	(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-methoxybenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]	387
18	(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-dimethylaminobenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]	330
19	(R)-[(2S,5R)-2-Methyl-5-methyl-4-(4-bromobenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]	435

Example 20

(R)-[4-(4-Cyanobenzoylamino)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperidine]

To a solution of (R)-[4-amino-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl) piperidine] (Example 21, 170 mg, 0.71 mmol) and triethylamine (0.12 ml, 0.86 mmol) in EtOAc (15 ml) was added a solution of 4-cyanobenzoylchloride (130 mg, 0.78 mmol) in EtOAc (10 ml). The resultant mixture was stirred at ambient temperature for 4 hours, washed with 1 M hydrochloric acid, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was chromatographed on silica with 50% EtOAc / DCM as eluent to give the title compound as a solid (97 mg, 0.26 mmol). NMR: 1.45 (m, 2H), 1.65 (s, 3H), 2.1 (m, 2H), 3.05 (m, 2H), 4.2 (m, 1H), 4.4-4.6 (m, 2H), 5.1 (s, 1H), 6.2 (d, 1H), 7.65 (d, 2H), 7.8 (d, 2H); m/z 368.

Example 21

(R)-[4-Amino-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperidine]

To a solution of 4-*t*-butyloxycarbonylaminopiperidine (Method C, 8.0 g, 40.0 mmol) and triethylamine (8.5 ml, 60 mmol) in DCM (200 ml) was added a solution of (S)-3,3,3-trifluoro-2-trimethylsilyloxy-2-methylpropanoyl chloride (*J. Med. Chem.*, 1999, *42*, 2741-2746) (10.1 g, 41.3 mmol) in DCM (50 ml). The resultant mixture was stirred at ambient temperature overnight, the DCM evaporated, the residue taken up in EtOAc (150 ml), washed with saturated citric acid solution, saturated sodium hydrogen carbonate solution and brine, dried and evaporated. The residue was dissolved in methanol (25 ml), treated with saturated hydrogen chloride in methanol (100 ml), stirred at ambient temperature overnight and evaporated to dryness. The residue was recrystallized from methanol / EtOAc to give the title compound as the hydrochloride salt (7.5 g, 27.2 mmol). Mp: 245-246°C; NMR: 1.45 (m, 2H), 1.5 (s, 3H), 1.95 (m, 2H), 3.25 (m, 1H), 4.4 (m, 2H), 4.65 (m, 2H), 7.15 (s, 1H), 8.2 (s, 3H); m/z (+ve ESP) 241 $(M+H)^+$.

Example 22

(R)-[(2S)-2-Methyl-4-(4-cyanobenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl) piperazine]

4-Cyanobenzoyl chloride (0.30 g) was added to a stirred solution of the (R)-[2-(S)-methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (Example 27; 0.40 g) and triethylamine (0.30 ml) in DCM (10 ml). The reaction mixture was allowed to stir at room temperature for 17 hours (overnight), and then partitioned between DCM (20 ml) and 2 M HCl (20 ml). The organic phase was separated, dried and concentrated to give a gum. The residue was purified by chromatography on an 8 g silica Biotage cartridge eluting 1:1 EtOAc / isohexane to give the title compound (0.445 g) as a white solid. NMR (DMSO-d_6, 100°C): 1.17 (d, 3H), 1.58 (s, 3H), 3.05-3.14 (m, 1H), 3.23-3.29 (m, 2H), 3.73 (brs, 1H), 3.88 (brs, 1H), 4.47 (d, 1H), 4.79 (brs, 1H), 6.79 (s, 1H), 7.58 (d, 2H), 7.88 (d, 2H); m/z 368.

Examples 23 - 25

The following compounds were prepared by the procedure of Example 22 using the appropriate benzoyl or sulphonyl chloride.

Ex	Compound	NMR (DMSO-d_6, 100°C)	M/z
23	(R)-[(2S)-2-Methyl-4-(4-*t*-butylbenzoyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl) piperazine]	1.11 (d, 3H), 1.32 (s, 9H), 1.52 (s, 3H), 3.03-3.10 (m, 1H), 3.20-3.26 (m, 2H), 3.83 (d, 1H), 3.94 (d, 1H), 4.47 (d, 1H), 4.76 (brs, 1H), 6.73 (s, 1H), 7.32 (d, 2H), 7.47 (d, 2H)	401 $(M+H)^+$
24	(R)-[(2S)-2-Methyl-4-(4-bromophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methyl-propionyl)piperazine]	1.23 (d, 3H), 1.50 (s, 3H), 2.40-2.47 (m, 1H), 2.56 (d, 1H), 3.14-3.20 (m, 1H), 3.45 (d, 1H), 3.61 (d, 1H), 4.58 (d, 1H), 4.85 (brs, 1H), 6.73 (s, 1H), 7.67 (d, 2H), 7.85 (d, 2H)	459
25	(R)-[(2S)-2-Methyl-4-(4-isopropylphenyl-sulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl) piperazine]	1.26 (d, 3H), 1.29 (d, 6H), 1.52 (s, 3H), 2.35-2.41 (m, 1H), 2.51 (d, 1H), 2.97-2.05 (m, 1H), 3.14-3.20 (m, 1H), 3.45 (d, 1H), 3.62 (d, 1H), 4.55 (d, 1H), 4.85 (brs, 1H), 6.76 (s, 1H), 7.50 (d, 2H), 7.70 (d, 2H)	421

Example 26

(R)-[(2S)-2-Methyl-4-(2-nitrobenzenesulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

To a stirred solution of (2S)-2-methyl-4-(2-nitrobenzenesulphonyl)piperazine (Method E; 14.1 g) in DCM (250 ml) at 0°C was added triethylamine (20 ml) followed by a dropwise addition of the a solution of (S)-3,3,3-trifluoro-2-(trimethylsilyloxy)-2- methylpropanoyl chloride (prepared from (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid (Method A) as described in *J. Med. Chem.*, 1999, **42**, 2741-2746) (12.5 g) in DCM (50 ml). The reaction mixture was allowed to stir at ambient temperature overnight and was washed with HCl (2 M, 200 ml). The organic phase was separated, dried and volatile material was removed by

evaporation to leave a pale yellow oil (25.97 g). This was re-dissolved in MeOH (250 ml) and HCl (2 M, 30 ml) was added and the reaction mixture was allowed to stir at ambient temperature overnight. Volatile material was removed by evaporation and the residue was partitioned between EtOAc (250 ml) and brine (200 ml). The organic phase was separated, dried and concentrated to leave a pale yellow glass (20.0 g). NMR: 1.32 (d, 3H), 1.68 (s, 3H), 2.77-2.88 (m, 1H), 2.98-3.03 (m, 1H), 3.46 (brs, 1H), 3.68 (d, 1H), 3.88 (d, 1H), 4.23 (brs, 1H), 4.89 (brs, 1H), 7.64-7.77 (m, 3H), 7.96 (d, 1H); m/z: 424.

Example 27

(R)-[(2S)-2-Methyl-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]

To a stirred solution of (R)-[(2S)-2-methyl-4-(2-nitrobenzenesulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine] (Example 26; 19.71 g) in anhydrous DMF (60 ml) was added thiophenol (5.5 ml) followed by anhydrous potassium carbonate (18.7 g). The reaction mixture was allowed to stir at ambient temperature under argon for 4 hours, filtered and washed with DCM (2 x 300 ml). The filtrate was acidified with HCl (2 M, 250 ml) and the organic phase was separated and discarded. The aqueous phase was adjusted to pH 8 with 2 M NaOH and extracted into EtOAc (5 x 300 ml). The organic layers were combined, dried and concentrated to give a pale yellow gum which slowly crystallised (4.88 g). NMR (DMSO-d_6, 100°C): 1.21 (d, 3H), 1.54 (s, 3H), 2.49-2.55 (m, 1H), 2.65-2.75 (m, 3H), 2.82-2.91 (m, 2H), 2.97-3.01 (m, 1H), 4.31 (d, 1H), 4.60 (s, 1H); m/z (+ve ESP): 241 $(M+H)^+$.

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Meth d A

(R)-(+)-2-Hydroxy-2-methyl-3,3,3-trifluoropropanoic acid

(R/S)-2-Hydroxy-2-methyl-3,3,3-trifluoropropanoic acid was resolved according to the resolution method described in European Patent Application No. EP 524781 (described for the preparation of the (S)-(-) acid) except that (1S, 2R)-norephedrine was used in place of (1R, 2S)-norephedrine or (S)-(-)-1-phenylethylamine to yield the title compound, $[\alpha]_D^{20}$ +18.1° (*c*, 8.8 in MeOH); NMR analysis of the acid in the presence of (R)-(+)-1-phenylethylamine gave an enantiomerical purity of >98%. NMR ($CDCl_3$): 1.27 (s, 3H) for the (R)-enantiomer, 1.21 (s, 3H) for the (S)-enantiomer.

Method B

5-(4-Methylsulphanylphenylsulphanyl)indoline

Tetrakis(triphenylphosphine)palladium(0) (0.99 g, 0.86 mmol) was added to a stirred solution of 5-bromoindoline (4.3 g, 21.7 mmol), 4-methylthiophenylthiol (3.4 g, 21.7 mmol) and sodium methoxide (2.4 g, 72.7 mmol) in anhydrous *n*-butanol (90 ml). The reaction mixture was heated under reflux with stirring for 6 hours then cooled and partitioned between EtOAc (200 ml) and brine (100 ml). The organic layer was separated, dried and volatile material was removed by evaporation. The residue was purified by flash column chromatography eluting with 0-30% EtOAc / *iso*-hexane to give the title compound (4.2 g, 15.3 mmol) as a solid. NMR: 2.43 (s, 3H), 3.03 (t, 2H), 3.6 (t, 2H), 6.58 (d, 1H), 7.05-7.27 (m, 6H); m/z (+ve ESP): 274 $(M+H)^+$.

Method C

4-*t*-Butyloxycarbonylaminopiperidine

1-Benzyl-4-*t*-butyloxycarbonylaminopiperidine (Method D, 5.4 g, 18.6 mmol) was dissolved in absolute ethanol (100 ml) and hydrogenated over 10% Pd / C for 24 hours at ambient temperature. The catalyst was removed by filtration and the filtrates evaporated to give the title compound (3.54 g, 17.7 mmol) which was used without further purification.

Method D

1-Benzyl-4-*t*-butyloxycarbonylaminopiperidine

To a stirred solution of 1-benzyl-4-aminopiperidine (3.8 g, 20 mmol) in water (20 ml) and *t*-butanol (20 ml) was added a solution of di-*t*-butyldicarbonate (5.24 g, 24 mmol) in *t*-butanol (20 ml). The mixture was heated at 50°C for 2 hours, cooled to ambient temperature, the *t*-butanol evaporated, the aqueous residue extracted with EtOAc (2 x 50 ml), the combined EtOAc extracts washed with brine, dried and evaporated to give the title compound which was used without further purification.

Method E

(2S)-2-Methyl-4-(2-nitrobenzenesulphonyl)piperazine

Sodium hydrogen carbonate (21.7 g) and acetone (50 ml) was added to a solution of (S)-(+)-2-methylpiperazine (6.0 g) in water (75 ml). The resulting suspension was cooled (0-5°C) and a solution of 2-nitrobenzenesulphonyl chloride (15.9 g) in acetone (25 ml) was added, the reaction mixture was allowed to stir at ambient temperature overnight. Water (60 ml) was added and volatile material was removed by evaporation. The residue was acidified to pH 2 by the addition of HCl (2 M, 75 ml) and the mixture was extracted into DCM (2 x 100 ml). The aqueous phase was adjusted to pH 10-11 by the addition of NaOH (2 M, 50 ml) and extracted into EtOAc (2 x 150 ml). The organic washings were combined, dried and concentrated to leave the title compound (14.1 g) as a yellow oil. NMR: 1.06 (d, 3H), 2.35-2.43 (m, 1H), 2.73-3.06 (m, 4H), 3.65-3.71 (m, 2H), 7.59-7.62 (m, 1H), 7.68-7.72 (m, 2H), 7.95-7.98 (m, 1H); m/z (+ve ESP): 286 $(M+H)^+$.

Example 28

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

5

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5
(e): Injection I	**(50 mg/ml)**
Compound X	5.0% w/v

1 M Sodium hydroxide solution	15.0% v/v
0.1 M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

Injection II	**10 mg/ml**
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1 M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

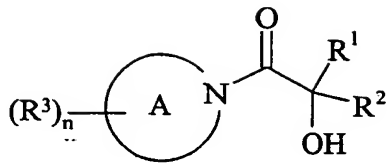
(g): Injection III	**(1 mg/ml,buffered to pH6)**
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

Ring A is a nitrogen linked mono or bicyclic heterocyclic ring; wherein if said heterocyclic group contains an -NH- moiety that nitrogen is optionally substituted by R^4-D-;

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently $C_k$alkyl optionally substituted by 1 to 2k+1 atoms selected from fluoro and chloro wherein k is 1-3;

or R^1 and R^2 together with the carbon atom to which they are attached, form a $C_m$cycloalkyl ring optionally substituted by 1 to 2m-2 fluorine atoms wherein m is 3-5;

$\mathbf{R^3}$ is a substituent on carbon and is halo, hydroxy, cyano, formyl, amino, nitro, carboxy, carbamoyl, ureido, thiol, sulphamoyl or R^5-E-;

$\mathbf{R^4}$ is C_{1-6}alkyl, phenyl or a heterocyclic group, wherein in R^4 any C_{1-6}alkyl, phenyl or heterocyclic groups (on a ring carbon) may be optionally substituted by one or more R^6 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8;

D is -C(O)-, -N(R^9)C(O)-, -S(O)$_2$-, -NS(O)$_2$-, -OC(O)- or D is a direct bond;

$\mathbf{R^5}$ is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, phenyl, naphthyl or a heterocyclic group, wherein in R^5 any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, phenyl, naphthyl or heterocyclic groups (on a ring carbon) may be optionally substituted by one or more R^6 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8;

E is -O-, -N(R^9)-, -C(O)-, -N(R^9)C(O)-, -C(O)N(R^9)-, -S(O)$_a$- wherein a is 0-2, -OC(O)-, -C(O)O-, -N(R^9)C(O)O-, -OC(O)N(R^9)-, -C(S)N(R^9)-, -N(R^9)C(S)-, -SO$_2$N(R^9)-, -N(R^9)SO$_2$-, -N(R^9)C(O)N(R^9)-, -N(R^9)C(S)N(R^9)-, -SO$_2$NHC(O)-, -SO$_2$N(R^9)C(O)-, -C(O)NHSO$_2$- or E is a direct bond;

R^6 is trifluoromethyl, C_{1-6}alkyl, halo, hydroxy, trifluoromethoxy, cyano, C_{1-6}alkoxy, formyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, *N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(*N*-C_{1-6}alkyl)amino, nitro, carboxy, carbamoyl, C_{1-6}alkoxycarbonyl, thiol, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$aminosulphonyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, ureido, *N'*-(C_{1-6}alkyl)ureido or *N'*-(C_{1-6}alkyl)$_2$ureido, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl, naphthyl, phenyl or a heterocyclic group wherein in R^6 any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cylcoalkyl, naphthyl, phenyl or heterocyclic groups (on a ring carbon) may be optionally substituted by one or more R^7 and if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^8;

R^7 is trifluoromethyl, cyano, C_{1-6}alkyl, halo, hydroxy, trifluoromethoxy, C_{1-6}alkoxy, formyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, amino, *N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(*N*-C_{1-6}alkyl)amino, nitro, carboxy, carbamoyl, C_{1-6}alkoxycarbonyl, thiol, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$aminosulphonyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl or a heterocyclic group (optionally substituted by one or more R^{11}), and wherein in R^7 any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cylcoalkyl groups may be optionally substituted by one or more groups selected from R^{12};

R^8 is C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzoyl, (heterocyclic group)carbonyl, phenylsulphonyl, (heterocyclic group)sulphonyl, phenyl or a carbon linked heterocyclic group, and wherein in R^8 any C_{1-6}alkyl, phenyl or heterocyclic group (on a ring carbon) may be optionally substituted by one or more R^6, and if a heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R^9 is hydrogen or C_{1-6}alkyl optionally substituted by one or more R^{10} with the proviso that R^{10} is not a substituent on the carbon attached to a nitrogen atom;

R^{10} is halo, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, *N*-(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(*N*-C_{1-6}alkyl)amino, C_{1-6}alkylsulphonylamino,

C_{1-6}alkylsulphonyl(*N*-C_{1-6}alkyl)amino, thiol, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)aminosulphonyl, *N*-(C_{1-6}alkyl)$_2$aminosulphonyl, carboxy, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl or formyl;

R^{11} is C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkoxyC_{1-6}alkanoyl, phenylC_{1-6}alkyl, benzoyl, phenylC_{1-6}alkanoyl, phenylC_{1-6}alkoxycarbonyl or phenylsulphonyl and wherein in R^{11} any C_{1-6}alkyl group can be optionally substituted by one or more R^{13};

R^{12} is halo, hydroxy, *N*-methylpiperazinyl, *N*-acetylpiperazinyl, morpholino, piperidino, cyano, amino, *N,N*-dimethylamino, acetamido, carbamoyl, carboxy, methanesulphonyl or sulphamoyl;

R^{13} is halo, hydroxy, cyano, amino, *N,N*-dimethylamino, acetamido, carbamoyl, carboxy, methanesulphonyl or sulphamoyl;

n is 0-5; wherein the values of R^3 may be the same or different;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof;

with the proviso that if R^1 is methyl, R^2 is trifluoromethyl and Ring A is piperazin-1-yl then $(R^3)_n$ is not i) 4-cyanobenzoyl, ii) 2-methyl-4-benzyloxycarbonyl, iii) 2-methyl, iv) 2-methyl-4-cyanobenzoyl, v) 2,5-dimethyl-4-benzyl, vi) 2,5-dimethyl or vii) 2,5-dimethyl-4-cyanobenzoyl.

2. A compound of formula (I) according to claim 1 wherein one of R^1 and R^2 is methyl and the other is trifluoromethyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

3. A compound of formula (I) according to either of claims 1 or 2 wherein Ring A is piperidyl, piperazinyl or indolinyl; wherein said piperazinyl is optionally substituted on nitrogen by R^4-D-;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

4. A compound of formula (I) according to any one of claims 1 to 3 wherein R^3 is a substituent on carbon and is selected from amino, methyl, 4-mesylphenylsulphonyl, 4-methylthiophenylthio, 4-fluorobenzoyl and 4-cyanobenzoylamino;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5. A compound of formula (I) according to any one of claims 1 to 4 wherein R^4 is C_{1-4}alkyl, phenyl {optionally substituted with one or more *t*-butyl, isopropyl, nitro, halo, *N,N*-dimethylcarbamoyl, *N,N*-dimethylamino, 2-hydroxyethylamino, cyano, acetyl, methoxy or carboxy} or thienyl;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

6. A compound of formula (I) according to any one of claims 1 to 5 wherein D is $-SO_2-$ or -C(O)-;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

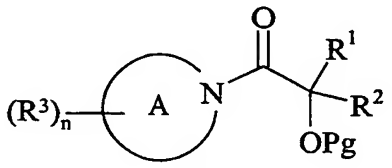
7. A compound of formula (I) according to any one of claims 1 to 6 wherein n is 0 - 3;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

8. A compound of formula (I) selected from:
(R)-[(2S,5R)-2-methyl-5-methyl-4-(4-carboxyphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine];
(R)-[(2S,5R)-2-methyl-5-methyl-4-(4-dimethylcarbamoylphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine];
(R)-[(2S,5R)-2-methyl-5-methyl-4-(4-fluorophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine];
(R)-{(2S,5R)-2-methyl-5-methyl-4-[4-(2-hydroxyethylamino)phenylsulphonyl]-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine};
(R)-[(2S,5R)-2-methyl-5-methyl-4-(4-cyanophenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine]; and
(R)-[(2S,5R)-2-methyl-5-methyl-4-(4-methoxyphenylsulphonyl)-1-(3,3,3-trifluoro-2-hydroxy-2-methylpropionyl)piperazine];

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

9. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process (in which variable groups are as defined for formula (I) unless otherwise stated) comprises of:

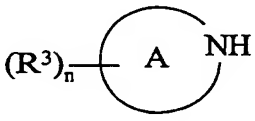
(a) deprotecting a protected compound of formula (II):



(II)

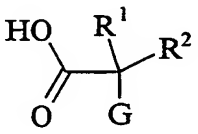
where Pg is an alcohol protecting group;

(b) coupling an amine of formula (III):



(III)

with an acid of formula (IV):



(IV)

wherein G is a hydroxyl group;

(c) coupling an amine of formula (III) with an activated acid derivative of formula (IV) wherein G is a hydroxyl group which may be protected as an ester or ether;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

10. A pharmaceutical composition which comprises a compound of formula (I) according to any one of claims 1 - 8, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester

thereof in association with a pharmaceutically-acceptable diluent or carrier.

11. A compound of the formula (I) according to any one of claims 1 - 8, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

12. The use of a compound of the formula (I) according to any one of claims 1 - 8, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for use in the treatment of diabetes mellitus, peripheral vascular disease and myocardial ischaemia in a warm-blooded animal such as a human being.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PHM.70590/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/03297	30/08/2000	04/09/1999
Applicant		
ASTRAZENECA AB		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   AMIDES AS INHIBITORS FOR PYRUVATE DEHYDROGENASE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (partially), 3-7 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claims 1, 3-7. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to issue a complete search report over the whole breadth of the claims.

The search and the search report may only be considered complete for claim 2 and all examples described in the application .

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/GB 00/03297

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/32 C07D295/22 C07D295/18 C07D209/08 C07D211/58
A61K31/495 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THOMAS D AICHER ET AL: "(R)-3,3,3-trifluoro-2-hdroxy-2-methylpropionamides are orally active inhibitors of pyruvate dehydrogenase kinase" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 42, no. 15, July 1999 (1999-07), pages 2741-2746, XP002122777 ISSN: 0022-2623 page 2741, left-hand column, line 24 -right-hand column, line 2 Scheme 1-3 --- -/--	1-7,9-12

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2001	14/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Diederen, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MANN, W. R. ET AL: "Diverse mechanisms of inhibition of pyruvate dehydrogenase kinase by structurally distinct inhibitors" BIOCHIM. BIOPHYS. ACTA (2000), 1480(1-2), 283-292 , XP000979112 figure 1 page 284, right-hand column, line 4 - line 8 table 1 ---	1-3,5-7, 10-12
P,X	AICHER ET AL.: "Secondary amides of (R)-3,3,3-Trifluoro-2-hydroxo-2-methylpropionicacid as inhibitors of pyruvate dehydrogenase kinase" J. MED. CHEM., vol. 43, no. 2, 27 January 2000 (2000-01-27), pages 236-49, XP002158429 table 2 page 236, right-hand column, line 8 - line 17 -----	1-7,9-12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1 (partially), 3-7 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for claims 1, 3-7. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

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